

### **REMARKS/ARGUMENTS**

Applicants will respond to the various items in the office action in the order they are presented.

#### *Information Disclosure Statement*

The examiner notes that the listing of references in the specification is not a proper Information Disclosure Statement. The specification reference listing was not intended to be a substitute for an Information Disclosure Statement. The references are presented as an aid to understanding the teaching set forth in the specification. Applicants are unaware of any prior art to the claims presented in this application. However, since the present application is a continuation of a parent application, for completeness of the record, Applicants will create and forward after this Response is filed an Information Disclosure Statement with the required fee setting forth all the patents which were cited in the parent application.

#### *Drawings*

Applicants do not believe any changes were made to the drawings.

#### *Specification*

The examiner has objected to the specification and required appropriate correction because the: "...description of the drawings at pages 20-21 do not address each portion of each figure individually, as required." The amendment to the specification presented corrects the figure descriptions and brings them into conformity with the issued parent patent.

The Examiner has required a new title for the invention that: "...is clearly indicative of the invention to which the claims are directed." In the initial filing of the present application,

the original title of the parent application/issued patent was retained. Applicants agree with the Examiner's observation that a more clearly indicative title is needed that reflects the present claims. Applicants have adopted the basic outline of the Examiner's suggested new title with modification to reflect the amendments made to the claims in response to the Examiner's claim rejection.

*Claim Rejections - 35 USC § 101*

The Examiner has rejected claim 1: "... under 35 USC § 101 because the claimed invention is directed to non-statutory subject matter." Applicants believe that the "selecting" step recited in the claim as filed led in part to the Examiner's conclusion that the claim was directed to non-statutory subject matter. As noted below, Applicants have responded to the Examiner's 35 USC § 112 rejections by amending the claim and presenting further claims to the same invention. Applicants respectfully respond that properly presented and construed claims of this type define statutory subject matter. The claims do much more than recite a manipulation of data. The claimed methods produce representative structures which can be compared and analyzed by various further methods. This is a concrete, tangible, and useful result. The claims also recite a method of characterizing the representative structures for comparative purposes. This also is a concrete, tangible, and useful result. Applicants submit that the amended and new claims are directed to statutory subject matter and respectfully request the Examiner to remove the 35 U.S.C. 101 rejection.

*Claim Rejections - 35 USC § 112*

The Examiner has rejected claim 1: "... under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In addition to the misspelling of the word "alignment", the Examiner states that:

"...the steps of the method fail to carry out the intent of the preamble. There are no steps which select any three dimensional conformations. It is not clear that the steps of the method provide for any three dimensional representation such that there are more than one to select from."

The Examiner further states:

"How is a representative structure determined? What is it representative of? Is it representative of all the three dimensional structures which could be generated? Is it representative of those three dimensional that are generated (but no such generation of structures is present in the claim)? Is it representative of the reactant molecules? Or of various combination of those reactant molecules that could possibly interact?"

Applicants note that the specification teaches that in order to compare the three dimensional shapes of the side chains (fragments) which reactant molecules would contribute to a combinatorially assembled molecule, there is needed some alignment procedure which allows such a comparison. Applicants teach the use of a topomeric alignment procedure which utilizes a set of canonical (or standardized) alignment rules. One such set of rules is set forth in the specification (page 38, line 15 to page 41, line 17). The topomeric alignment method is a

method of generating a conformation (shape) of each fragment which can then be usefully compared to the conformation (shape) of other similarly aligned fragments. The conformation generated by topomeric alignment is the representative conformation of the fragment (page 38, lines 5-6); that is, it is the comparable conformation. The topomeric alignment may or may not resemble the conformation of the fragment in the chemical world. The specification notes (page 38, lines 7-9) that: "...the prior art inherently teaches away from the idea because the topomerically derived conformers often may be energetically inaccessible and incapable of binding to any receptor." The advance over the prior art of the present invention is that such topomerically generated conformation are highly useful for shape comparison.

Applicants appreciate the Examiner's remarks and understand the possible confusion or misdirection created by the use of the term "selecting" in the preamble. The claim has been amended to recite "generating" instead of "selecting." This use is consistent with the language of the specification (page 38, line 15). Further, Applicants have amended the claim to recite more clearly that the application of the alignment rule generates the representative conformation.

The Examiner has also stated:

"Further, in claim 1, the term 'defining' lacks concrete, specific instruction as to how to carry out such a step. Similarly the term 'applying' in the claim. Both the 'defining' step and the 'applying' step lack sufficient detail in how they are to be carried out in order to accomplish the goal of the preamble."

With the amendment to the term "generating" in place of "selecting" Applicants submit that the claim more specifically addresses the Examiner's concern. However, Applicants

respectfully submit that the term "defining" will be clearly understood by those skilled in the art in view of the specification. As noted above, a preferred topomeric alignment procedure is taught (defined) in the specification (page 38, line 15 to page 41, line 17). Applicants teach that in appropriate circumstances other alignment rules could be used:

"The idea of a topomeric conformer is that it is rule based. The exact rules may be modified for specific circumstances. In fact, once it is appreciated from the teaching of this invention that a particular topomeric protocol is useful (yields a valid molecular descriptor), other such protocols may be designed and their use is considered within the teaching of this disclosure." (page 38, lines 10-14).

In view of the above teachings, Applicants submit that to those skilled in the art the claim does not lack concrete, specific instructions with respect to the step of defining.

Applicants also respectfully submit that the step of "applying" will be clearly understood by those skilled in the art in view of the specification. The specification teaches a specific example of applying a topomeric alignment. In addition, the amendment to the claim now recites the result of the "applying" step. Applicants submit that the claim as amended does distinctly state and claim the subject matter of applicants invention.

Finally, in addition to amendment of claim 1, Applicants present new claims 2 - 10. Claims 4 - 8 of U.S. Patent No. 6,185,506 cover a method of characterizing the three dimensional structure of reactants using topomeric alignment. The common inventive principal contained in the claims of the issued patent and the present application is the use of a topomeric alignment procedure to define comparable conformations. The present application was filed to

more fully claim the application of the topomeric alignment method.

Applicants respectfully request the Examiner to remove the 35 U.S.C. 112 rejection.

*Claim Rejections - 35 USC § 102*

The Examiner has rejected claim 1:

"...under 35 U.S.C. 102(b) as being anticipated by Cramer, III et al. (USP 5,307,287 - of record in 08/592132).

The claim is drawn to methods of selecting three dimensional conformers of reactants through topological alignment.

Cramer, III et al. (USP 5,307,287) disclose methods of generating topomeric alignment rules, and applying them to reactants. See at least Figure 6, column 7 lines 5-49, column 11 line 49 to column 13 line 56, columns 19-21, computer code appendices, claims 45-65."

Applicants must respectfully disagree with the Examiner's statement that Crammer, III et al. disclose methods of topomeric alignment of reactants. The starting point for a CoMFA analysis is the alignment of conformers of compounds that all have a measured activity for the same receptor. CoMFA does not treat reactants (side chains or fragments) but rather deals with entire molecules. This is unlike the present application where it is not known whether a given reactant when coupled with a core will result in a compound with activity at a specified receptor. The topomeric alignment procedure forces all reactant fragments into the same overall alignment (whether or not the shape resulting from that alignment is energetically accessible or active at any receptor) so that their shapes can be compared. CoMFA alignment procedures, on the other

hand, start by (sometimes arbitrarily) choosing one conformation of a first molecule (in the series of molecules all having measurable activity at the same receptor) and then aligning the remaining molecules in the series to the first molecule using various methods discussed in the CoMFA patent. The alignment of subsequent molecules is always to a first selected molecule. The present invention does not teach the alignment of subsequent molecules to a first selected molecule. CoMFA does not utilize a rule based alignment as taught in the present application. The present application clearly discusses and distinguishes the CoMFA alignment and topomeric alignment approaches at page 36, lines 6 - 21. Finally, there is nothing comparable in the present invention to the Field Fit alignment methodology cited by the Examiner at column 11, line 49 to column 13, line 56.

Accordingly, Applicants respectfully submit that Crammer, III et al. (USP 5,307,287) does not anticipate the claims of the present application. Applicants respectfully request the Examiner to remove the 35 U.S.C. 102 rejection.

The Examiner has also rejected claim 1:

"...under 35 U.S.C. 102(b) as being anticipated by Cramer, III et al. (USP 5,025,388 - of record in 08/592132).

The claim is drawn to methods of selecting three dimensional conformers of reactants through topological alignment.

Cramer, III et al. (USP 5,307,287) disclose and claim methods of selecting three dimensional conformers of reactants through topological alignment.

Serial No. 09/776,708  
Amendment dated Sept. 8, 2003  
Reply to Office Action of Mar. 6, 2003

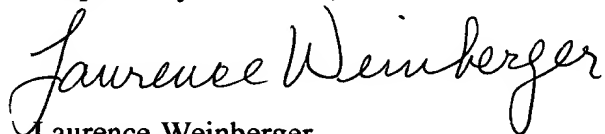
See at least columns 6-7, columns 11-16, columns 19-20, and claims 1-5, 21-34, 62-75."

The presently cited Cramer '388 patent is the parent of the '287 patent discussed above. It contains the same disclosure with respect to alignment methods. In response to this rejection, Applicants incorporate and restate their above remarks to the rejection based on the '287 patent. For the same reasons, Applicants respectfully submit that Crammer, III et al. (USP 5,025,388) does not anticipate the claims of the present application. Applicants respectfully request the Examiner to remove the 35 U.S.C. 102 rejection.

Applicants submit that they have adequately addressed all grounds for rejection raised by the Examiner and respectfully request that a timely Notice of Allowance be issued in this case.

September 8, 2003

Respectfully submitted,



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